NATIONAL INSTITUTES OF HEALTH

Pharmacy Update

January/February 2000

Drug Information Service
Department of Pharmacy
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

Clopidogrel (Plavix®): A Brief Review

Introduction

Inhibitors of platelet function have been associated with decreased morbidity in patients with established atherosclerotic cardiovascular disease. Aspirin, a weak inhibitor of platelet function, has been shown to be effective in preventing and reducing acute coronary syndromes. More recently, glycoprotein (GP) IIb/IIIa inhibitors have been introduced as potent inhibitors of platelet activation. These agents are effective in reducing coronary events when given in combination with percutaneous intervention (PCI). Thienopyridines, a new class of antiplatelet agents, achieve moderate levels of platelet inhibition by interfering with the adenosine diphosphate (ADP) receptor site. Subsequently, this disrupts the binding of adenosine 5′-diphosphate to its platelet receptor. Ticlopidine (Ticlid®), the first FDA-approved thienopyridine, exerts its effect by inhibiting ADP-induced platelet-fibrinogen binding and has been used for the secondary prevention of stroke. However, ticlopidine's use has been limited by the risk of neutropenia and agranulocytosis. Clopidogrel (Plavix®) is the second antiplatelet in the thienopyridine class.

Indications

Clopidogrel is indicated for the reduction of atherosclerotic events (e.g., myocardial infarction, stroke, vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral artery disease. Ticlopidine is approved for the secondary prevention of stroke. Clopidogrel achieves its effect by irreversibly modifying the platelet ADP receptor. This leads to a selective and irreversible inhibition of ADP-induced platelet aggregation and affects ADP-dependent activation of the GPIIb/IIIa complex, which is the primary receptor for fibrinogen present on the platelet surface. Clopidogrel's effect on platelets is maintained for the lifespan of the platelet (7-10 days) because of irreversible binding. This mechanism is different from that of other platelet inhibitors.

Clopidogrel must be biotransformed in vivo to an active metabolite in order to exert its pharmacological actions. The effects of clopidogrel are demonstrated within 2 hours after an oral dose. Steady-state platelet inhibition is reached within 3 to 7 days of treatment. At steady-state concentrations achieved with clopidogrel 75 mg administered orally once daily, the average platelet inhibition is between 40 and 60 percent. Recently, reports have suggested loading patients with clopidogrel in order to achieve steady-state concentrations more rapidly. A small study (n=10) revealed that patients given clopidogrel 375 mg orally achieved desired antiaggregatory effects (55 percent platelet inhibition) within 1 hour of the dose. This effect was subsequently maintained with 75 mg daily. Platelet aggregation slowly returns to normal in approximately 5 days when therapy is discontinued. However, some sources suggest the effects of clopidogrel can last for 7 to 10 days. The manufacturer recommends clopidogrel treatment be discontinued 7 days prior to elective surgery when an antiplatelet effect is not desired.

Selected Clinical Trials

The pivotal study evaluating the efficacy of clopidogrel is known by the acronym CAPRIE (Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events). This study was an international, multi-center, randomized, double-blind trial comparing clopidogrel 75 mg administered orally once daily and aspirin 325 mg administered orally once daily to

evaluate their efficacy in reducing the risk of ischemic stroke, myocardial infarction, or vascular death. More than 19,000 patients with recent ischemic stroke (within 1 week to 6 months), recent myocardial infarction (within 35 days), or documented peripheral vascular disease (intermittent claudication and ankle/arm systolic BP ratio ≤ 0.85; or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty) were enrolled. Patients treated with clopidogrel had a 5.32 percent risk per year of ischemic stroke, myocardial infarction, or vascular death compared with 5.83 percent in the aspirin group. The overall relative risk was reduced by 8.7 percent in favor of clopidogrel ($p = 0.043$).

In populations similar to those enrolled in the CAPRIE study, clopidogrel 75 mg administered orally once daily would be expected to prevent 24 major clinical events for every 1000 patients treated for one year. In comparison, aspirin 325 mg administered orally once daily would prevent 19 major events for every 1000 patients treated for one year.

Precautions and Contraindications

Clopidogrel is contraindicated in patients with active pathological bleeding. Clopidogrel is extensively metabolized by the liver. Therefore, it should be used with caution in patients with severe liver disease. The elimination half-life of clopidogrel is 8 hours, with approximately 50 percent of the drug excreted in the urine and 46 percent in the feces. Use of this agent is contraindicated in patients with hypersensitivity to ticlopidine. It is important to note that the structures of clopidogrel and ticlopidine are very similar. Therefore, if a patient experiences hypersensitivity to one, there is a likelihood of cross-reactivity to the other.

Adverse Events

Side effects observed in approximately 5 percent of patients treated with clopidogrel include: indigestion, nausea, bleeding disorders, rash, diarrhea, and pruritus. The incidence of gastrointestinal bleeding is 2 percent with clopidogrel and 2.7 percent with aspirin. Aspirin and clopidogrel share similar adverse effect profiles.

Dosage and Administration

The recommended initial dose of clopidogrel is 75 mg administered orally once daily with or without food. It is important to realize that clopidogrel exhibits a dose-dependent antiplatelet effect (i.e., the antiplatelet effect is increased with an increase in dose). No dosage adjustment is needed in the elderly or renally impaired.

Conclusion

Clopidogrel is a new antiplatelet agent indicated for the reduction of atherosclerotic events (e.g., myocardial infarction, stroke, vascular death). Data from the CAPRIE trial suggest that clopidogrel is as safe and effective as aspirin in reducing atherosclerotic events. Unlike ticlopidine, clopidogrel appears to be free of serious hematologic adverse effects.

References available upon request.

Sirolimus (Rapamune®): A Brief Review

Introduction

Sirolimus is a new immunosuppressant with a novel mechanism of action. It is immunologically synergistic with cyclosporine-based regimens. Combination with cyclosporine may provide enhanced efficacy and may require lower target cyclosporine concentrations, thus potentially minimizing cyclosporine nephrotoxicity.

Description

Sirolimus is available as an oral solution containing sirolimus 1 mg/mL in 60-mL bottles, 150-mL bottles, and 1-, 2-, and 5-mL unit-of-use pouches. Inactive ingredients include Phosal 50PG, polysorbate 80, and ethanol.

Indication

Sirolimus is indicated for the prevention of organ rejection in patients receiving renal transplants. It is recommended that sirolimus be used in a regimen with cyclosporine and corticosteroids.

Pharmacology

Sirolimus is structurally related to tacrolimus and has immunosuppressive properties. Sirolimus blocks cytokine-induced T- and B-cell activation. Tacrolimus (FK-506) and cyclosporine inhibit the production of cytokines. Intracellularly, sirolimus forms a complex with cytosolic FK-binding proteins (FKBPs; immunophilins). This complex causes cell-cycle arrest (G1 to S phase) by modulating the activity of a key regulatory kinase, sirolimus effector protein (SEP) or Target of Rapamycin (ToR), without affecting calcineurin phosphatase activity.

Pharmacokinetics

Sirolimus is rapidly absorbed, with a mean time-to-peak concentration (T_{max}) of 1 to 2 hours. The bioavailability is approximately 14 percent. Food (fatty meals) decreases the C_{max} but increases the T_{max} and AUC.

The volume of distribution is large (12 ± 7.5 L/kg) with extensive distribution into blood elements. Sirolimus is highly (92 percent) bound to proteins. Sirolimus is a substrate for cytochrome P4503A4 and p-glycoprotein and is extensively metabolized. Using radiolabelled drug, the majority (92 percent) was found in the feces with only 2 percent excreted in the urine. The terminal half-life is estimated to be 62 ± 16 hours.

Mild hepatic impairment (Child-Pugh A or B) decreases sirolimus clearance and prolongs the half-life to 79 ± 12 hours; dose adjustment (reduction by one-third) is recommended in this population. Only a minimal amount (2 percent) of sirolimus is excreted in the urine; no dose adjustments are suggested in patients with impaired renal function.

Clearance is slightly lower in males ($t_{1/2}$: 72 h) compared to females ($t_{1/2}$: 61 h), but dose adjustments based on gender are not recommended. No significant

differences in trough concentrations were found in black and non-black patients, and no race-specific dose adjustments are currently recommended.

Routine blood concentration monitoring is not suggested. Populations to consider for monitoring should include pediatric patients, patients with hepatic impairment, and patients taking CYP 3A4 inducers or inhibitors. Close monitoring is also recommended when cyclosporine is discontinued or its dosage reduced. Using a radioimmunoassay, mean trough whole blood sirolimus concentrations were 9 ng/mL with the 2 mg per day dose and 17 ng/mL with the 5 mg per day dose.

Selected Clinical Trials

Sirolimus 2 mg per day and 5 mg per day has been studied in two randomized, double-blind, multicenter controlled trials in renal transplant patients. In one trial, the control group was treated with azathioprine, and in the second trial, the control group received placebo. In both trials, all patients received cylcosporine and corticosteroids concurrently. Efficacy failure (biopsy-proven rejection episode, graft loss, or death) assessed at 6 months post-transplant was used as the primary endpoint in both studies (Table 1). Both of the sirolimus dosage regimens significantly reduced the incidence of the primary endpoint.

Table 1.

	Treatment	N	Efficacy Failure (%)
Study 1	Sirolimus 2 mg/day	284	18.7
	Sirolimus 5 mg/day	274	16.8
	Azathioprine 2-3 mg/kg/day	161	32.3 *P* <0.025
Study 2	Sirolimus 2 mg/day	227	30.0
	Sirolimus 5 mg/day	219	25.6
	Placebo	130	47.7 *P* <0.025

In both studies, the major reason for efficacy failure was a biopsy-proven rejection episode. Sirolimus reduced the incidence of all grades of rejection. Both patient and graft survival at 12 months post-transplant were similar in the sirolimus and control groups.

In the study that used azathioprine as the control arm, patients were stratified by race at entry. In black patients compared to non-black patients, efficacy failure was similar for sirolimus 2 mg per day (34.9 percent, n=63) and azathioprine (33.3 percent, n=42), but lower for sirolimus 5 mg per day (18 percent, n=61). In the placebo-controlled study where prospective race stratification did not occur, efficacy failure in black patients was similar for both sirolimus doses and placebo.

In an exploratory phase II study, sirolimus plus either standard- or reduced-dose cyclosporine (Sandimmune formulation) was compared to full-dose cyclosporine therapy. Corticosteroids were administered to all patients in accordance with standard transplant procedures. Patients who received full-dose cyclosporine plus either sirolimus 1 mg/m^2 per day or 3 mg/m^2 per day (C+S; n=47) had a significantly lower rate of biopsy-proven acute rejection at 6 months (8.5 percent) versus patients who received full-dose cyclosporine (C) alone (n=25, 32 percent, p=0.018). A similar significant difference (p< 0.05) was found at 12 months; the incidence in C+S-treated patients was 10.6 percent and in C patients was 32 percent. When compared to cyclosporine (32 percent), there was no difference in rejection incidence at 6 months for all patients treated with sirolimus plus low-dose cyclosporine (19.5 percent, p=0.27). However, in non-African Americans the rejection rate was 10.7 percent.

Adverse Effects

Comparative adverse reaction data is available in renal transplant patients receiving sirolimus 2 mg per day (n=499), sirolimus 5 mg per day (n=477), azathioprine (n=160), or placebo (n=120). All patients received cyclosporine and corticosteroids concommitantly.

Adverse reactions that occured more commonly compared to the control group with all sirolimus dosages include hypercholesterolemia, hypertriglyceridemia, hypertension, and rash. With sirolimus 5 mg per day, significant adverse effects relative to the control arm include anemia, arthralgia, diarrhea, hypokalemia, and thrombocytopenia. Compared to sirolimus 2 mg per day, sirolimus 5 mg per day is associated with an increased incidence of anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever, diarrhea, and mucocutaneous herpes simplex infection.

Drug Interactions

Sirolimus is a substrate for cytochrome P4503A4 and p-glycoprotein, and thus many drug interactions are possible. When given at the same time as modified cyclosporine oral capsules (Neoral® soft gelatin capsules), the sirolimus C_{max} increased by 116 percent and AUC increased by 230 percent compared to sirolimus administered alone. When sirolimus was given 4 hours after modified cyclosporine oral capsules, C_{max} increased by 37 percent and AUC increased by 80 percent when compared to sirolimus administration alone. Increased trough concentrations (by 67-86 percent) were also noted when sirolimus was administered at the same time as cyclosporine oral solution compared to sirolimus administered alone. Sirolimus does not appear to affect cyclosporine trough concentrations in kidney transplant patients until 6 months post-transplant; lower cyclosporine doses may be required to achieve the same target cyclosporine concentration at that time.

Based on single-dose pharmacokinetic interaction studies, drugs that can be administered without sirolimus dosage adjustment include acyclovir, digoxin, glyburide, nifedipine, norgestrel/ethinyl estradiol, prednisolone, and sulfamethoxazole/trimethoprim. Diltiazem, ketoconazole, and rifampin can substantially alter the pharmacokinetic disposition of sirolimus and should generally not be used in combination with this drug.

Precautions and Contraindications

Lymphocele occurred more commonly in sirolimus-treated patients. Hyperlipidemia (increased cholesterol and triglycerides) occurs frequently with sirolimus treatment and may require treatment in 42 to 52 percent of patients. Sirolimus-treated patients should routinely be monitored for hyperlipidemia. Patients treated with cyclosporine and sirolimus had higher serum creatinine concentrations

compared to controls. Renal function should be monitored carefully and caution should be exercised if other nephrotoxic agents are used. Kidney transplant recipients who are immunosuppressed by sirolimus therapy are at increased risk for infection. Pnuemocystis carinii and cytomegalovirus prophylaxis should be given for 12 months and 3 months after transplantion, respectively.

Mild hepatic impairment (Child-Pugh A or B) decreases sirolimus clearance and prolongs the half-life (to 79 ± 12 hours); dose adjustment (reduction by one-third) is recommended in this population. No dose adjustments are required in patients with impaired renal function.

Sirolimus is classified as pregnancy category C. Effective contraception should be initiated before sirolimus is started, used during sirolimus treatment, and used for 12 weeks after sirolimus is discontinued.

Dosage and Administration

It is recommended that sirolimus be administered in a regimen containing cyclosporine and corticosteroids. Sirolimus is administered orally. The dose should be diluted in either orange juice or water (not grapefruit juice). Sirolimus should be administered consistently either with or without food. The manufacturer recommends that sirolimus be administered 4 hours after the modified cyclosporine dosage forms (solution or capsules).

The recommended loading dose is 6mg, followed by a maintenance dose of 2 mg per day (loading dose should be 3 times the maintenance dose). A loading dose of 15 mg, followed by 5 mg per day was also used in clinical trials. This dosage was found to be safe and effective. It, however, was not more effective than the 6 mg/2 mg regimen, and was associated with more toxicity. Doses of 3 mg/m^2 (loading) and 1 mg/m^2 (maintenance) should be used in patients ≥ 13 years old and who weigh less than 40 kilograms.

Conclusion

Sirolimus is a novel immunosuppressive agent that complements currently available agents for the prophylaxis of acute rejection in renal transplant recipients. It has the potential to reduce cyclosporine dosage requirements, thereby possibly reducing cyclosporine-related nephrotoxicity. Its adverse effect profile compares favorably with that of other available immunosuppressive agents.

References available upon request.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Clopidogrel (Plavix®), an oral antiplatelet agent
- Losartan (Cozaar®), an oral angiotensin II receptor antagonist
- Sirolimus (Rapamune®), an oral immunosuppressive drug
- Loteprednol (Lotemax®), an ophthalmic corticosteroid
- Carvedilol (Coreg®), an oral beta-receptor antagonist
- Ramipril (Altace®), an oral angiotensin converting enzyme inhibitor

Deletions

- Ticlopidine (Ticlid®)
- Labetalol [Oral form only] (Normodyne® or Trandate®)
- Enalapril (Vasotec®)

Editor's Note

We wish to thank Reem A. Abo-Zena, Pharm.D. and Barry R. Goldspiel, Pharm.D., for their contributions to this issue of Pharmacy Update.

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar